

Effects of Nedocromil Sodium and Placebo Delivered by Pressurised Aerosol in Bronchial Antigen Challenge

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Nedocromil sodium (Tilade®) is the disodium salt of a pyranoquinoline dicarboxylic acid developed for the treatment of chronic obstructive airways disease (2). The new compound has been shown to inhibit the immediate bronchoconstrictor response induced by exercise (4, 5) and sulfur dioxide (1) challenge and early clinical studies indicate that nedocromil sodium is an effective drug for the treatment of extrinsic and intrinsic asthma (3, 6). The aim of the present study was to compare the protective effect of nedocromil sodium (4 mg administered by pressurised aerosol) and placebo, against the allergen-induced early asthmatic reaction. A double blind crossover design was employed, with patients randomly assigned to active or placebo treatment according to a latin square design.

MATERIAL AND METHODS

Eleven patients entered the trial (8 males and 3 females). Patients' ages ranged from 18 to 44 years with a mean of 30 years. All patients had a history of allergic asthma with relevant positive skin test or RAST. Allergy to seasonal antigens was tested for and, if demonstrated, tests were performed outside the season. Lung function was above 75% of predicted normal value. All patients were reasonably well controlled with bronchodilator and/or sodium cro-

moglycate or inhaled steroids. All patients had a stable and cooperative personality and were able to perform the techniques necessary to measure ventilatory function. None of the patients had other diseases of significance besides allergy. Similarly, no significant abnormalities in haematologic or clinical biochemical data were found. Patients with late reactions, unstable asthma, or a history of acute exacerbations were excluded. Also excluded were patients whose pretreatment ventilatory function test varied from one occasion to another by more than 15% (FEV_1). None of the patients was pregnant.

A dose titration scheme was followed to determine a PD_{20} - FEV_1 (i.e. an antigen dose giving a 20% decrease in FEV_1) value on each occasion. The patients attended for an initial control day and 2 treatment days prior to which they had abstained from the use of oral bronchodilators for 24 h, sustained theophyllines for 48 h and inhaled bronchodilators for 8 h. Treatment with inhaled corticosteroides was continued unchanged with the exception that no morning dose was given on a challenge day. Doubling dose of antigen was used to determine the PD_{20} - FEV_1 value. Arrangements were made for patients to attend the study days at weekly intervals at the same time of day. On the two challenge days, two baseline measurements of lung function were made with a 5 min interval.

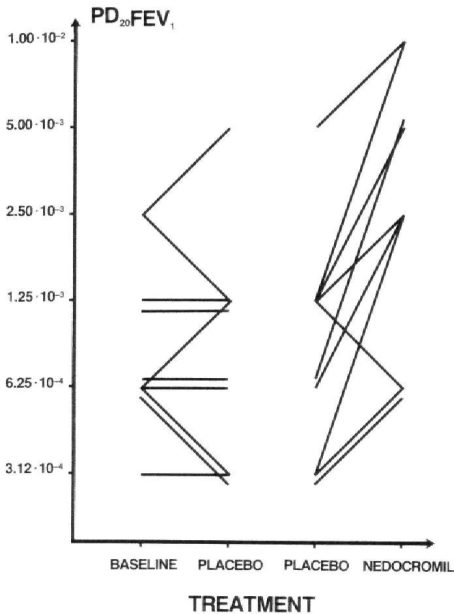


Fig. 1 shows the allergen dose giving a 20% decrease in the postsaline FEV_1 value after inhalation of 2 puffs of either placebo or nedocromil sodium administered by pressurised aerosols. A higher dose was necessary to give a decrease in the pulmonary function in 9 of 10 patients treated with nedocromil sodium compared with two of 10 after placebo treatment. $PD_{20}\text{-}FEV_1$ is expressed in terms of w/v.

FEV_1 was measured as the highest of three maximally forced expiratory manoeuvres (FEV_1 within 5% variation). After a further 5 min, one of the trial treatments was administered (i.e. 2 puffs) and the lung functions test was repeated at 5, 10, 20, 30 min after treatment. Thirty minutes after treatment, the antigen challenge was performed by titration with doubling doses of antigen given at intervals of 10 min with FEV_1 readings 0, 5 and 10 min after each dose until a decrease of $\geq 20\%$ FEV_1 was recorded. The PD_{20} values were calculated on a logarithmic scale by linear interpolation, using the measurement recorded after the antigen dose which produced $\geq 20\%$ fall and the measurement recorded after the preceding dose.

Statistical significance was assessed at the 5% level using two-tailed tests. Repeated measures analyses of variance, which take account of patient and treatment effects, were used.

RESULTS

One patient was withdrawn from the study because of technical problems; the others completed the study. There was no change in FEV_1 when the average FEV_1 values obtained 5 and 10 min before treatment were compared with the average values 5 and 10 min after treatment and with the average values 20 and 30 min after treatment. The results of the antigen challenges on the 3 different days are shown in Fig. 1. Statistical significance ($P < 0.01$) was found between the treatments in favour of nedocromil sodium. The two methods of FEV_1 calculation gave similar results. The mean $PD_{20}\text{-}FEV_1$ after treatment with nedocromil sodium was approximately 4 times greater than after placebo. None of the patients had unusual symptoms or adverse reactions.

Conclusion Nedocromil sodium was found to be effective in preventing a fall in pulmonary function after antigen challenge. Further studies are now needed to investigate the long-term effects of the drug in the treatment of asthma, and also to compare the efficacy of nedocromil sodium with the effects of other well-known and commonly used antiasthmatic drugs, such as beta 2-agonists, sodium cromoglycate, and beclomethasone dipropionate.

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